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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,979	02/22/2002	Phillip Dan Cook	ISIS-5028	9967

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,979	COOK ET AL.	
	Examiner	Art Unit	
	Amy H Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/3/2002,9/23/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-16, in the telephonic interview on 12/02/2004 is acknowledged.

The requirement for restriction is still deemed proper and is therefore made FINAL.

Claims 17-22 have been withdrawn, as being drawn to non-elected inventions. Applicant timely traversed the restriction (election) requirement in the telephonic interview on 12/02/2004.

Claim Objections

Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 8 is drawn to the method of claim 6, wherein said oligonucleotide is an antisense oligonucleotide. The oligonucleotide of claim 6 is specified to be an antisense oligonucleotide.

Claims 3, 4, 9 and 10 are objected to as being dependent on rejected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-8 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to methods of modulating the expression of a nucleic acid in the hepatic system of a mammal and to methods of treating an animal having a hepatic disease or disorder associated with a protein encoded by a gene comprising administering an oligonucleotide which hybridizes to the gene, wherein the oligonucleotide has sterol moieties. Although the specification is enabling for preferential targeting to the hepatic system via an antisense oligonucleotide with two cholesterol moieties *in vivo*, it does not provide enablement for the predictable and preferential targeting via oligonucleotides with any sterol moiety *in vivo,* nor does it provide enablement for the treatment of an animal *in vivo*. It is unpredictable whether other sterols would function to preferentially target the hepatic system, as shown with cholesterol. Given the divergent nature of compounds claimed, it is unclear that other sterols would function like cholesterol, due to differences in structure that may affect the uptake of the sterol. Additionally, different sterols may target different tissues and the effective concentration needed of the sterol may differ to result in the same effect. Although the specification overcomes the issue of delivery, the treatment methods of claims 12-16 are very broad and encompass diseases and disorders that would be

associated with the hepatic system, but not with antisense oligonucleotide inhibition. For example, diseases or disorders that are associated with down regulation of a protein encoded by a gene would not be treated by an inhibitor such as an antisense oligonucleotide. Additionally, in many cases, it has not been determined which specific genes are associated with a given disease or disorder. Although the specification is enabled for the in vivo inhibition of a nucleic acid via an antisense oligonucleotide conjugated to cholesterol, it is not enabled for the treatment of a sufficient number of hepatic diseases or disorders in a sufficient number of organisms.

The state of the prior art is such that gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration. Although applicant has demonstrated delivery, utilizing the method for treatment is unpredictable.

The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Branch (TIBS 1998, vol. 23, p. 45-50), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNS can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established.... clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in a sufficient number of organisms, with a resultant inhibition of gene expression, as claimed. The specification provides examples antisense oligonucleotide inhibition of a target nucleic acid, i.e. MDR1, *in vivo* in mice (specification page 113); however, these results are not necessarily predictive of *in vivo* inhibition resulting in treatment of other organisms or other genes.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides with sterol moieties *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful treatment and inhibition of expression of a given target gene. One of skill in the art would not know how to deliver oligonucleotides to an organism in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic

applications in any organism. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for preferential targeting to the hepatic system via an antisense oligonucleotide with two cholesterol moieties *in vivo*, the specification is not enabling for the scope of claims 1, 2, 5-8 and 11-16, which encompass the *in vivo* inhibition of any gene via an antisense oligonucleotide with any sterol in any organism as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. Although applicant has demonstrated that the use of two cholesteryl moieties has provided unexpected and unpredictable delivery results, applicant has not shown a correlation between cholesterol and any other sterol. The addition of sterol moieties further produces unpredictability due to steric differences, which may lower the inhibitory effect of the compound. As demonstrated by by Letsinger et al., the addition of two sterol moieties does not necessarily enhance delivery. Letsinger et al. teach that anchoring a cholesteryl fragment to an oligonucleotide significantly enhances the antiviral activity, but anchoring a second cholesteryl fragment leads to a reduction in activity (see table 2). Claims 14 and 15 are rejected as they are drawn to the method of treatment. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1, 2, 5-8 and 11-16 are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 recites the limitation "said mammal" in line 4. There is insufficient antecedent basis for this limitation in the claim, which is drawn to a method of treating an animal.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,753,423. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain methods with overlapping scope.

The instant invention is drawn to a method of modulating the expression of a nucleic acid in the hepatic system of a mammal, comprising administering to said

mammal an oligonucleotide which hybridizes to said nucleic acid to modulate the expression of said nucleic acid, wherein said oligonucleotide has at least two sterol moieties covalently bonded thereto; and to a method of preferentially targeting an antisense oligonucleotide to liver cells in a mammal comprising covalently bonding said oligonucleotide to at least two sterol moieties to form a sterol-oligonucleotide conjugate and administering said sterol-oligonucleotide conjugate to said mammal to preferentially target said liver cells to modulate the expression of a gene in said liver cells.

Patent '423 teaches a method of modulating the expression of a nucleic acid, which encompasses preferentially targeting, in the hepatic system of a mammal, comprising the step of administering to said mammal a compound to modulate the expression of said nucleic acid. Claim 2 of patent '423 encompasses any of a number of formulas, wherein R_{1a} and R_{1b} could each comprise cholesterol. Additionally, the substituent is at a 2'O-position, a 3'O-position or a 5'-O position of a nucleoside. The instant claims contain overlapping scope with claim 2 of patent '423. Therefore, the instant methods would have been obvious over the methods of patent '423.

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 of copending U.S. Patent Application No. 2004/0142899. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain methods with overlapping scope.

Application '899 teaches a method of modulating the expression of a nucleic acid in the hepatic system of a mammal in need of hepatic gene modulation, which encompasses preferential targeting, comprising the step of administering to said mammal a compound to modulate the expression of said nucleic acid. This method is drawn to targeting an antisense oligonucleotide to hepatic tissues in a mammal in need of hepatic gene modulation, which encompasses the method of treatment of the instant claims. Claim 3 of application '899 encompasses any of a number of formulas, wherein R_{1a} and R_{1b} could each comprise cholesterol. Additionally, the substituent is at a 2'O-position, a 3'O-position or a 5'-O position of a nucleoside. Claim 3 of application '899 contains overlapping scope with the instant claims. Therefore, the instant methods would have been obvious over the methods of patent '899.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:30 am – 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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